Amendments to the Specification

In the specification, please replace the paragraph beginning at line 6 on page 24 with the following paragraph:

Figures 1A-C are schematics showing nanotips for intracellular recordings according to one aspect of the invention. Figure. 1A shows an example of ~~a~~ hollow nanotip 2 formed from a pulled capillary. Figure 1B shows an array of pulled capillaries mounted together using a holder. Figure 1C shows ~~a~~ one-dimensional array 3 of microfabricated nanotips.

In the specification, please replace the paragraph beginning at line 11 on page 24 with the following paragraph:

Figures 2A-D show nanotip-based electrode systems according to another aspect of the invention. Figure 2A shows a nanotip filled with an electrolyte solution. The electrolyte solution is in contact with a working electrode. Figure 2B shows a nanotip filled with an electrolyte solution and a diffusion-barrier mounted in the tip. Figure 2C shows a nanotip filled with ~~a~~ solid-state conducting material 4, such as a metal, a carbon fiber or a solidified conducting polymer. Figure 2D shows a nanotip filled with a conducting polymer hydrogel.

In the specification, please replace the paragraph beginning at line 18 on page 24 with the following paragraph:

Figures 3A-C illustrate conducting solid-state material based nanoelectrodes according to a further aspect of the invention. Figure 3A shows an example of a carbon fibre electrode coated with an insulating material to reduce measurement noise. The apex of the nanotip is uncoated in order to ensure electrical contact. Figure 3B shows a silver-coated carbon-fibre nanoelectrode. Figure 3C shows an example of microfabricated array solid-state nanoelectrodes. Figure 3C shows array 3 of capillaries mounted together, nanotips 2 and substrate 5.

In the specification, please replace the paragraph beginning at line 3 on page 25 with the following paragraph:

Figures 5A-F show methods of using nanoelectrodes according to one aspect of the invention. Nanoelectrode~~s~~ 1 may be inserted into cells using a stab-injection protocol as illustrated in Figures 5A-C. Here, only mechanical force (F) is used to break the cellular membrane. Figures 5D-F show use of a micro-electroinjection protocol to insert the nanoelectrodes. Here, a combination of mechanical force and electrical voltage pulses (V) are used to promote breakdown of cellular membranes facilitating nanoelectrode insertion.

In the specification, please replace the paragraph beginning at line 10 on page 25 with the following paragraph:

Figure 6 illustrates parallel registration of electrical properties in a plurality of adherent cells 6 using a plurality of nanoelectrodes. Array 3 of nanoelectrodes is shown.

In the specification, please replace the paragraph beginning at line 12 on page 25 with the following paragraph:

Figures 7A-C show the insertion of nanoelectrodes into cells grown in suspension. In one aspect, cells are held in place with holding capillaries through the application of a negative pressure on the holding pipette. Figure 7A shows nanoelectrode insertion into ~~a~~ cell 6 in suspension that is held in place using a holding pipette. Figure 7B shows an array of holding pipettes for positioning cells 6 in register with ~~an~~ array 3 of nanoelectrodes on a substrate. Figure 7C shows the use of a porous substrate to maintain ~~the~~ cells 6 in a relatively stationary position for insertion of ~~an~~ array 3 of nanoelectrodes.

In the specification, please replace the paragraph beginning at line 19 on page 25 with the following paragraph:

FIGS. 8A-B show different modes of electrophysiological registration. In FIG. 8A, one nanoelectrode is inserted into ~~a~~ cell 6 while another electrode is placed outside the cell and is used as a reference electrode. FIG. 8B shows a three-electrode set-up comprising one external reference electrode and two measurement electrodes inserted into ~~a~~ cell 6.

In the specification, please replace the paragraph beginning at line 3 on page 26 with the following paragraph:

Figures 10A-D illustrate nanoelectrodes that are coupled to microfluidic devices. Figures 10A and 10B show top and side views, respectively, of a microfluidic chip having a "spokes wheel" design. As can be seen in Figure 10A, the chip comprises a substrate with a plurality of microfluidic channels 8 whose inlets are radially disposed about the circumference of ~~a~~ measurement chamber 7 which contains ~~a~~ nanoelectrode 1-impaled or nanoelectrode 1-contacted cell 6. Solution through the channels can be regulated (e.g., by pressure and/or voltage differentials) to provide for sequential delivery of drug candidates into the measurement chamber. In order to register the action of the drug candidates on the cell, a nanoelectode is inserted into the cell to measure changes in its electrical properties. Figure 10B shows an enlarged view of ~~the~~ measurement chamber 7 and the insertion of ~~a~~ nanoelectrode 1 into ~~the~~ cell 6 as it is exposed to solution flow from ~~a~~ microchannel 8 L7. Substrate (5) is shown. Figures 10C-D show top and side views, respectively of a chip-based nanoelectrode having a similar spokes wheel design. In this embodiment, the nanoelectrode is part of the chip itself (see, Figure 10D).

In the specification, please replace the paragraph beginning at line 17 on page 26 with the following paragraph:

Figures 11A-D illustrate a system for scanning a cell impaled with a nanoelectrode across multiple collimated streams containing drug candidates. As shown in Figure 11A, ~~a~~ substrate 5 comprising a plurality of channels 8 which feed into a cell chamber is placed in proximity to ~~a~~ nanoelectrode 1 and holding pipette 9. Proper positioning of ~~a~~ cell by ~~the~~ holding pipette 9 and/or insertion of ~~a~~ nanoelectrode 1 into ~~the~~ cell 6 can be visualized by making the cell chamber at least partially optically transparent so that light absorbed and/or transmitted by the cell can be measured. ~~The n~~ Nanoelectrode 1 is used to measure the electrical properties of ~~the~~ cell 6 as it is scanned across microchannel inlets that open into the cell chamber (see, e.g., as show in Figures 11B-D).

In the specification, please replace the paragraph beginning at line 6 on page 27 with the following paragraph:

Figure 13 is a perspective view of a kit in accordance with one aspect of the invention illustrating a process for dispensing fluids from 96-well plates onto a microfluidic chip substrate 5 comprising interdigitating reservoirs using automated array pipettors and cell delivery using a pipette.

In the specification, please replace the paragraph beginning at line 10 on page 27 with the following paragraph:

Figures 14A-C comprise a top view of a microfluidic chip structure for HTS of drugs according to one aspect of the invention, for scanning a sensor such as a nanoelectrode-impaled cell or cells across interdigitated ligand and buffer streams. Figure 14A depicts the overall chip substrate 5 structure for both a 2D and 3D microfluidic system. Figure 14B shows an enlarged view of the reservoirs of the chip and their individual connecting channels 8. Figure 14C shows an enlarged view of interdigitating microchannel whose outlets intersect with the measurement chamber of the chip.

In the specification, please replace the paragraph beginning at line 17 on page 27 with the following paragraph:

Figure 15A schematically depicts a top view of ~~the~~ interdigitating channels 8 of a microfluidic chip, with ~~a~~ nanoelectrode 1-impaled or nanoelectrode 1-contacted cell 6 being moved past the outlets of the channels. Figures 15B and 15C depict side views of alternate embodiments of the outlets and microchannels. FIGS. 15B and 15C are side views showing a 2D and 3D microfluidic chip design, respectively. FIG. 15D is a perspective view of a 3D chip design according to one aspect of the invention, in which the chip comprises a bottom set and top set of channels. Figure 15E is a side view of Figure 15D, showing fluid flow can be controlled through pressure differentials so that fluid flowing out of a channel 8 in the bottom set will make a "U-turn" into an overlying channel. Figure 15F is a top view of Figure 15D and shows cell scanning across the "U-turn" fluid streams where microchannels 8 are shown.

In the specification, please replace the paragraph beginning at line 4 on page 28 with the following paragraph:

Figures 17A-N are schematics showing chip designs for carrying out cell scanning across ligand streams using buffer superfusion to provide a periodically resensitized sensor. Figure 17A is a perspective view of the overall chip design and microfluidic system. Nanoelectrode 1 is shown. Figures 17B-G show enlarged views of the outlets of microchannels and their positions with respect to a superfusion capillary and a nanoelectrode-contacted cell, as well as a procedure for carrying out cell superfusion while scanning a nanoelectrode-contacted cell across different fluid streams. "P" indicates a source of pressure on fluid in a microchannel or capillary. Bold arrows indicate direction of movement. Substrate 5 is shown. Figures 17H-17N show a different embodiment for superfusing cells. As shown in the perspective view in FIG. 17H, instead of providing capillaries for delivering buffer, a number of small microchannels placed at each of the outlets of the ligand delivery channels are used for buffer delivery. As ~~a~~ nanoelectrode 1-contacted cell 6 is moved to a ligand channel and

the system detects a response, a pulse of buffer can be delivered via the small microchannels onto the cell for superfusion. The advantage to using this system is that varying the delay time between signal detection and buffer superfusion can precisely control the exposure time of the nanoelectrode-contacted cell to a ligand. Figure 17I is a cross-section through the side of a microfluidic system used in this way showing proximity of a nanoelectrode-contacted cell to both ligand and buffer outlets. Figure 17J is a cross section, front view of the system, showing flow of buffer streams. Figure 17K is a cross-section through a top view of the device showing flow of ligand streams and placement of the buffer microchannels. Figures 1-7M show use of pressure applied to a ligand and/or buffer channel to expose a nanoelectrode-contacted cell to ligand and then buffer.

In the specification, please replace the paragraph beginning at line 27 on page 28 and continuing to page 29 line 4, with the following paragraph:

Figures 18A-I are top views of microchannel outlets in relationship to a nanoelectrode 1-contacted cell, 6 collectively showing different methods by which a nanoelectrode-contacted cell can be moved in relation to the fluid streams. Figures 18A-C show mechanical scanning of the nanoelectrode-contacted cell across stationary microchannel outlets. Figures. 18D-F show mechanical scanning of microchannel outlets relative to a stationary nanoelectrode-contacted cell. Figures 18G-I show a method for sweeping fluid streams across an immobilized nanoelectrode-contacted cell by controlled variation of the pressure across, and flow rates through, each individual microchannel.

In the specification, please replace the paragraph beginning at line 5 on page 29 with the following paragraph:

Figures 19A-C are top views of one design of a microfluidic chip for carrying out cycles of rapid delivery and withdrawal of compounds into and from a cell chamber for housing a nanoelectrode-contacted cell. Figure 19A shows the overall arrangements of the

microchannels feeding the cell chamber. Figure 19B is an expanded view of reservoirs 12 and the individual channels 8 through which they are accessed. Figure 19C shows an enlarged view of microchannel outlets that feed into the cell chamber.

In the specification, please replace the paragraph beginning at line 11 on page 29 with the following paragraph:

Figure 20 is an enlarged top view of the cell chamber of FIG. 19A, depicting the arrangement of microchannels 8 around a cell chamber 7 comprising a nanoelectrode-contacted cell 6.